

WHAT IS CLAIMED IS:

- 1 1. A method of increasing the efficiency of transformation of cycling cells,
2 said method comprising:
- 3 synchronizing cells at a first stage of the cell cycle, and
- 4 transforming said cells at a second stage of the cell cycle within about
5 one cell cycle of said first stage with a nucleic acid that encodes a desired gene product.
- 1 2. A method of claim 1 wherein cells are synchronized by contacting said
2 cells with an amount of a cell cycle synchronizer that is effective to synchronize cells at said
3 first stage of the cell cycle.
- 1 3. A method of claim 2 wherein said cell cycle synchronizer synchronizes
2 cells at a stage of the cell cycle when the nuclear membrane is substantially degraded.
- 1 4. A method of claim 1 wherein said cell cycle synchronizer synchronizes
2 cells at late S phase.
- 1 5. A method of claim 1 wherein said cell cycle synchronizer synchronizes
2 cells at the G₂/M phase boundary.
- 1 6. A method of claim 1 wherein said cell cycle synchronizer synchronizes
2 cells at a stage other than M phase, and the nucleic acid accumulates in cells that have cycled to
3 the G₂/M phase boundary.
- 1 7. The method of claim 1 wherein said cell cycle synchronizer is a vinca
2 alkaloid.
- 1 8. The method of claim 1 wherein said cell cycle synchronizer is cisplatin.

- 1 9. The method of claim 1 wherein said cell cycle synchronizer is selected
2 from the group consisting of taxol and taxolene.
- 1 10. A method of claim 1 wherein said first stage and said second stage are the
2 same.
- 1 11. A method of claim 1 wherein said nucleic acid encodes a therapeutic gene
2 and said therapeutic gene is foreign to the cell.
- 1 12. A method of claim 11 wherein the gene product of the therapeutic gene is
2 toxic to the cell.
- 1 13. A method of claim 12 wherein the gene product of the therapeutic gene
2 induces apoptosis.
- 1 14. A method of claim 1 wherein the nucleic acid is part of a lipid-nucleic acid
2 particle.
- 1 15. A method of inhibiting the growth of cancer cells, said method
2 comprising:
3 administering to a cancer patient an amount of a cell cycle synchronizer
4 that is effective to synchronize cancer cells of said patient at a first stage of the cell cycle;
5 and
6 administering to said cancer patient a nucleic acid that transforms
7 cancer cells of said patient;
8 wherein the expression of said nucleic acid inhibits the growth of said
9 cancer cells.
- 1 16. A method of claim 15 wherein said cancer cells are synchronized at a
2 stage when the nuclear membrane is substantially degraded.

1 17. A method of claim 15 wherein said cell cycle synchronizer synchronizes
2 the cell cycle at late S phase.

1 18. A method of claim 15 wherein said cell cycle synchronizer synchronizes
2 the cell cycle at the G₂/M interphase.

1 19. A method of claim 15 wherein said cell cycle synchronizer synchronizes
2 the cell cycle at a stage other than M phase, and the nucleic acid accumulates in cells when a
3 plurality of cells exposed to the agent have cycled to the G₂/M interphase.

1 20. A method of claim 15 wherein said cell cycle synchronizer is a vinca
2 alkaloid.

1 21. A method of claim 15 wherein said cell cycle synchronizer is cisplatin.

1 22. A method of claim 15 wherein said cell cycle synchronizer is selected
2 from the group consisting of taxol and taxolene.

1 23. A method of claim 15 wherein said first stage and said second stage are
2 the same stage of the cell cycle.

1 24. A method of claim 15 wherein said nucleic acid encodes a therapeutic
2 gene.

1 25. A method of claim 24 wherein the therapeutic gene is foreign to the
2 patient.

1 26. A method of claim 25 wherein the gene product of the therapeutic gene is
2 toxic to said cells.

1 27. A method of claim 26 wherein the gene product of the therapeutic gene
2 induces apoptosis of said cells.

- 1 28. A method of claim 15 wherein the nucleic acid is part of a lipid-nucleic
2 acid particle.
- 1 29. A method of claim 15 wherein the nucleic acid is administered
2 systemically.
- 1 30. A method of claim 24 wherein the therapeutic gene is expressed in said
2 cancer cells.
- 1 31. A method of claim 30 wherein the therapeutic gene is HSV-TK and
2 ganciclovir is also administered to said cancer patient.
- 1 32. A method of claim 15 wherein said cell cycle synchronizer is administered
2 prior to administering said nucleic acid.
- 1 33. A method of claim 31 wherein said cell cycle synchronizer is administered
2 at least 32 h prior to administering said nucleic acid.
- 1 34. A method of claim 31 wherein said cell cycle synchronizer is administered
2 at least 48 h prior to administering said nucleic acid.
- 1 35. A method of claim 15 wherein said nucleic cid is administered prior to
2 administering said cell cycle synchronizer.
- 1 36. A method of claim 15 wherein said nucleic acid is administered at least
2 32 h prior to administering said cell cycle synchronizer.
- 1 37. A method of claim 15 wherein said nucleic acid is administered at least
2 48 h prior to administering said cell cycle synchronizer.
- 1 38. A method of enhancing the therapeutic effect of a foreign therapeutic
2 gene administered to a patient, ~~said method comprising the steps of~~

Accepted for publication

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- 3 (a) administering a cell cycle blocking agent to said patient; and
4 (b) administering said foreign therapeutic gene to said patient within
5 seven days of step (a).

1 39. The method of claim 38 wherein step (b) is performed within 3 days of
2 step (a).

1 40. The method of claim 38 wherein step (b) is performed within 24 hours
2 of step (a).

1 41. The method of claim 38 wherein said foreign therapeutic gene is a
2 plasmid.

1 42. The method of claim 38 wherein said foreign therapeutic gene
2 comprises a gene selected from the group consisting of genes encoding a cytokine, apoptotic
3 protein, tumor suppressor, heat shock protein, immunogenic antigen, proteinase inhibitor,
4 anti-angiogenic protein, suicide gene for use in GDEPT, ribozyme, antisense nucleic acid,
5 viral protein and a toxin.

1 43. The method of claim 38 wherein said foreign therapeutic gene is
2 administered systemically.

1 44. The method of claim 38 wherein said foreign therapeutic gene is
2 administered locally or regionally.

1 45. The method of claim 38 wherein said foreign therapeutic gene is fully
2 encapsulated in a lipid formulation such that less than 5% of the gene is degraded after
3 exposure of said formulation to 1 U DNase I for 30 minutes in digestion buffer at 37°C.

1 46. The method of claim 38 wherein said cell cycle blocking agent is
2 selected from the group consisting of DNA alkylating agents, DNA topoisomerase
3 inhibitors, microtubule assembly inhibitors, microtubule disassembly inhibitors, DNA-cross
4 linking agents, DNA-binding agents and nucleoside analogues.

sub D² 47. The method of claim 38 wherein said ~~cell cycle blocking agent~~ is selected from the group consisting of cyclophosphamide, etoposide, taxol, vincristine, cisplatin, doxorubicin and 5-fluorouracil.

48. The method of claim 38 wherein said cell cycle blocking agent is in a liposome formulation.

sub E³ 49. A method of claim 38 wherein said cell cycle blocking agent is administered prior to administering said foreign therapeutic gene.

50. A method of claim 38 wherein said cell cycle blocking agent is administered at least 32 h prior to administering said foreign therapeutic gene.

51. A method of claim 38 wherein said cell cycle blocking agent is administered at least 48 h prior to administering said foreign therapeutic gene.

52. A method of claim 38 wherein said foreign therapeutic gene is administered prior to administering said cell cycle blocking agent.

53. A method of claim 38 wherein said foreign therapeutic gene is administered at least 32 h prior to administering said cell cycle blocking agent.

54. A method of claim 38 wherein said foreign therapeutic gene is administered at least 48 h prior to administering said cell cycle blocking agent.

sub E² 55. A method of enhancing the therapeutic effect of a cell cycle blocking agent, or of lowering the dosage of a cell cycle blocking agent required for a therapeutic effect, administered to a patient comprising the steps of: (a) administering said cell cycle blocking agent to a patient; and (b) administering a foreign therapeutic gene to said patient within seven days of step (a).

add E³

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